Brightline-2: MDM2–p53 antagonist BI 907828 in patients with advanced, MDM2-amplified, TP53 wild-type BTC, PDAC or other selected solid tumours

John Bridgewater, 1,2 Teresa Macarulla, 2 Chigusa Morizane, 3 Kazuyoshi Ohkawa, 4 Makoto Ueno, 5 Arndt Vogel, 6 Joy Hu, 7 Michael Teufel, 8 Angela Märtén, 9 Lipika Goyal, 10 Changhoon Yoo 11

1Department of Medical Oncology, UCL Cancer Institute, London, UK; 2Vail of Hebrón University Hospital and Vail of Hebrón Institute of Oncology (VHH), Barcelona, Spain; 3Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital, Tokyo, Japan; 4Department of Hepatobiliary and Pancreatic Oncology, Osaka International Cancer Institute, Osaka, Japan; 5Department of Gastroenterology, Kanagawa Cancer Center, Yokohama, Japan; 6Department of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany; 7Boehringer Ingelheim (People’s Republic of China) Investment Co., Ltd., Shanghai, China; 8Boehringer Ingelheim Pharmaceuticals Inc, Ridgefield, CT, USA; 9Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany; 10Stanford Cancer Center, Palo Alto, CA, USA; 11Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Introduction

Mechanism of action of BI 907828, an MDM2–p53 antagonist

- Inactivation of p53 is a key mechanism by which tumours promote survival and proliferation.
- MDM2, an E3 ubiquitin ligase, is an endogenous negative regulator of p53.
- BI 907828 blocks the interaction between p53 and its negative regulator MDM2. This stabilises p53, permitting p53 target gene induction, leading to cell cycle arrest or apoptosis in TP53 wild-type tumour cells.

MDM2 amplification prevalence

- MDM2 is amplified in a range of tumour types, including biliary tract carcinoma and pancreatic ductal adenocarcinoma.

Trial rationale

- Advanced biliary tract carcinoma and pancreatic ductal adenocarcinoma are associated with a median survival of ~1 year in the advanced stages, and effective therapies are needed.
- In two ongoing Phase I studies (1403-0001, 1403-0002), treatment with BI 907828 + ezabeutinib (an anti-PD-1 antibody) was associated with initial signs of activity in selected advanced/metastatic solid tumours.

Efficacy summary and swimmer plot of patients with BTC treated in two Phase Ia/b trials (1403-0001/1403-0002)

- In 10 patients with biliary tract carcinoma who received BI 907828 as monotherapy (n=6), or in combination with ezabeutinib (n=4), the objective response rate was 50% and three patients achieved stable disease as best response.
- Disease control lasting 26 months was observed in six out of 10 patients.

Objectives

Primary
- Evaluate efficacy of BI 907828, objective response rate
- Evaluate efficacy: duration of response, progression-free survival, overall survival

Secondary
- Evaluate health-related quality of life: EORTC-QLQ-C30, EORTC QLQ-BIL21 (Cohort 1) and others

Inclusion and exclusion criteria

Inclusion

- Locally advanced or metastatic:
  - Biliary tract carcinoma
  - Pancreatic ductal adenocarcinoma
  - Lung adenocarcinoma
  - Bladder cancer

- Receipt of appropriate prior standard-of-care therapy

Written report confirming MDM2 amplification (copy number ≥8)

TP53 wild-type

≥1 measurable lesion (RECISt v1.1)

ECOG performance status of 0/1

Adequate organ function

Exclusion

- Previous administration of BI 907828 or any other MDM2–p53 or MDMX (MDM4)–p53 antagonist
- Major surgery performed ≤4 weeks prior to treatment on trial or planned ≤6 months after screening
- Previous or concomitant malignancies that may affect treatment efficacy or trial outcome
- Use of restricted medications or drugs likely to interfere with safe conduct of the trial
- Receiving treatment for brain metastases or leptomeningeal disease that may interfere with assessment of trial endpoints

Endpoints

Primary
- Objective response rate by central independent review (RECISt v1.1)
- Duration of response and progression-free survival based on central independent review
- Overall survival

Secondary
- Disease control
- Occurrence of adverse events and treatment-related adverse events while on treatment

References

7. Yamamoto N, et al. ASCO 2023;Suppl 1, Abstract 3946

Presented at the AMMF’s Hybrid 2023 European Cholangiocarcinoma Conference, Essen, UK, 10-12 May, 2023

This study was funded by Boehringer Ingelheim. The authors were fully responsible for all content and editorial decisions, were involved at all stages of poster development and have approved the final version.

The authors did not receive payment related to the development of this poster. Medical writing support for the development of this poster, under the direction of the authors, was provided by Jim Sinclair PhD of Ashfield MedComms, an Inizio Company, and funded by Boehringer Ingelheim